UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/731,961 | 12/10/2003 | Richard Voellmy | | 4563 |

7590 04/25/2005

Richard Voellmy
Avenue des Cerisiers 39B
Pully, 1009
SWITZERLAND

| EXAMINER | |
|---|---|
| BURKHART, MICHAEL D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/731,961 | VOELLMY, RICHARD | |
| | Examiner | Art Unit | |
| | Michael D. Burkhart | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Specification*

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example, pages 30-31) . Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 11 recite modified viruses whose genome includes a gene switch "and a small molecule regulator". It cannot be determined if the viral genome includes a gene switch and a small molecule regulator (i.e. encodes a small molecule regulator), or if the gene switch requires heat and a small molecule regulator in order to be activated. Therefore, the metes and bounds of the claimed subject matter are unclear. It would be remedial to specify that the viruses include a gene switch "wherein the gene switch is activated by heat and a small molecule regulator", or that the small molecule regulator is encoded by the viruses. This rejection affects all dependent claims.

Claims 1, 6, 11, and 16 recite the limitation "efficient replication" regarding modified viruses. It cannot be determined what constitutes "efficient" replication. For example, would replication at 10% of wild-type levels be considered "efficient"? Is 20% "efficient"? Therefore, the metes and bounds of the claimed subject matter are unclear. This rejection affects all dependent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-13 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants claim a pair of modified viruses whose combined genomes contain all genetic information required for conditional replication of the virus pair and include a gene switch controlling expression of a viral protein required for replication of the viral pair. Applicants disclose the requirements of such a pair of adenoviruses. The claims read on a very large genus of potential virus pairs and viral proteins required for replication from any viral family. The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure

and function, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

In the instant case, applicants only disclose a pair of modified adenoviruses with E1A, E1B or E4 under control of the gene switch. Neither applicants nor the prior art disclose the claimed viral pairs wherein each member of the pair is from a different family. In this situation each virus is unable to complement the genetic deficiencies found in the other member and only one is able to be complemented by the viral protein under control of the gene switch. To use one of applicants examples, if adenoviral E1A where the claimed viral protein required for replication under control of the gene switch, how could this E1A complement a modified retrovirus? Furthermore, applicants state (page 12, lines 1-4) that "...when a pair of viruses is used, the viruses are typically of the same species. The underlying reason is that...at least one virus of the virus pair is dependent for replication on species-specific viral proteins expressed from ...the other virus". Given this species-specific requirement, how can there be a basis for one skilled in the art to envision embodiments other than the disclosed adenoviral pair and E1 and E4 proteins? Even if the disclosed adenoviruses (which have not been reduced to practice) were accepted as an embodiment of a "virus pair" for the instant invention, there is no structural/functional basis provided to envision other embodiments. Applicants claim pairs of modified viruses whose combined genomes contain all genetic information required for conditional replication by function only, without a correlation between structure and function. The prior art does not compensate for the lack of description of specific examples of the claimed virus pairs. The lack of disclosure and broad genus regarding the claimed "pair of modified

viruses" would require the skilled artisan to conclude that the example presented by the applicants are not sufficient to describe the claimed genus.

Claims 11-13 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pair of modified adenoviruses, does not reasonably provide enablement for a pair of modified viruses from separate families or species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art. The art concerning producing a pair of modified viruses (from different families) whose combined genomes contain all genetic information required for conditional replication of the virus pair and include a gene switch controlling expression of a viral protein required for replication of the viral pair is unpredictable. Because viruses from different families encode completely distinct proteins, it is unpredictable that one modified virus would express the genes needed to complement a virus from a different family. Applicants state (page 12, lines 1-4) that "...when a pair of viruses is used, the viruses are typically of the same species. The underlying reason is that...at least one virus of the virus pair is dependent for replication on species-specific viral proteins expressed from ...the other virus". Chester et al

(Nat. Biotech., 2002) establish that modified viruses from different virus families require complementation by different genes (from within the respective viral family). Whereas expression of E1 genes in 293 cells complements E1-defective adenovirus, additional genes are required to complement conditionally replicative retroviruses. Specifically, Chester et al use 293INT cells that express retroviral GAG and POL proteins (p. 261, first column) to complement defective retroviruses based on pBABE-puro (Figure 1). Therefore, the genes required to complement E1-deleted adenoviruses (i.e. found in typical 293 cells) are not sufficient to complement the modified retroviruses, which require the expression of retroviral genes *gag* and *pol* by the 293INT cells.

State of the art. The state of the art regarding the production of a pair of modified viruses (from different families) whose combined genomes contain all genetic information required for conditional replication of the virus pair and include a gene switch controlling expression of a viral protein required for replication of the viral pair, is poorly developed. The development of such modified viruses would have to be done empirically, along with the development of the appropriate cell lines.

Number of working examples. Applicants have provided no working examples of the claimed invention, only a prophetic example of a pair of modified adenoviruses dependent upon conditional expression of E1 or E4 genes for replication.

Amount of guidance. Applicants provide no direction for modified virus pairs wherein the viruses come from different families or species. The specification requires the skilled artisan to practice trial and error experimentation with modification of different viruses, essential viral proteins, vectors, and cell lines to determine which (if any) will be compatible as claimed.

Scope of the invention. The claims are broad in nature and read on any combination of modified viral pairs from any viral family reliant upon expression of any viral protein required for replication.

Nature of the invention. The invention involves the unpredictable art of producing a pair of modified viruses (from different families) whose combined genomes contain all genetic information required for conditional replication of the virus pair and include a gene switch controlling expression of a viral protein required for replication of the viral pair.

Level of skill in the art. While the level of skill in the art is high, the unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

***Conclusion***

No claims are allowed.

The closest prior art is exemplified by Emiliusen et al (Gene Therapy, 2001) and Wagstaff et al (Euro. J. Neuro., 1998). Emiliusen et al disclose a retroviral vector comprising a heat-shock element (HSE) linked to the TYR-300 promoter, but this HSE-TYR-300 transcription control element is not linked to expression of a viral protein required for replication, but rather to

a cytotoxic gene (i.e. GALV envelope protein, see Fig. 7a). Similarly, Wagstaff et al use an adenovirus vector to deliver a heat shock factor (HSF1) to cells, but no viral proteins are under transcriptional control of a heat shock element.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael D. Burkhart
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER